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Relationship between formaldehyde and quaternium-15 contact allergy. Influence of strength of patch test reactions

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Background: In groups of patients with formaldehyde allergy, many have positive patch tests to quaternium-15. Conversely, of patients allergic to quaternium-15, over half also react to formaldehyde.

Objectives: To test our hypothesis that patients with stronger patch test reactions to formaldehyde are more likely to react to quaternium-15, attesting to the aetiological role for formaldehyde in such co-reactivity.

Methods: Retrospective analysis of all patients patch tested with formaldehyde and quaternium-15 in the European baseline series between 1994 and 2009 (TRUE test®).

Results: In a group of 86 patients allergic to formaldehyde, 73% co-reacted to quaternium-15; in the subgroup of 70 women, the percentage was 83. In both groups, more reactions were observed to quaternium-15 in the patients with a ++ reaction compared to the patients with a + reaction to formaldehyde. Conversely, stronger reactions to quaternium-15 were significantly more often associated with formaldehyde sensitivity in a group of 107 patients reacting to quaternium-15 and a subgroup of 88 women. In men, such effects were not observed and only 5 of 16 (31%) men allergic to formaldehyde also reacted to quaternium-15.

Conclusions: In women, but not in men, stronger reactions to formaldehyde lead to more positive quaternium-15 patch tests.

Key words: contact allergy; co-reactivity; formaldehyde; quaternium-15. © John Wiley & Sons A/S, 2010.

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The preservative quaternium-15 is a formaldehyde-releaser; in the presence of water, formaldehyde is split off from the parent molecule by hydrolysis. The relationship between positive patch tests to quaternium-15 and formaldehyde contact allergy is well known. Of patients with a positive patch test to quaternium-15, over half co-react to formaldehyde. Conversely, some 40% of all patients with formaldehyde sensitivity also react to quaternium-15. We have previously suggested that reactions to quaternium-15 in formaldehyde-sensitive individuals are caused by formaldehyde that is either present in the patch test materials or is released from it in the water-containing skin (1). Whether a reaction to quaternium-15 is observed may simply depend on whether the threshold for elicitation of a reaction to formaldehyde can be reached (2). If this assumption is correct, patients with stronger reactions to formaldehyde (++ or +++) should more often co-react to quaternium-15 than in the case of weaker reactions (+), attesting to the etiological role for formaldehyde in such co-reactivity. The aim of this study was to test this hypothesis.

Materials and Methods

We reviewed the data of all patients seen in the contact dermatitis unit of the Department of Dermatology of the University Medical Centre Groningen between June 1994 and June 2009 and patch tested with the baseline series, containing both formaldehyde and quaternium-15 (TRUE test®, Allerderm, Phoenix AZ, USA). The concentration of formaldehyde is 0.18 mg/cm^2 and that of quaternium-15 is 0.1 mg/cm^2. The amount of formaldehyde that can theoretically be released from the quaternium-15 patch test is about 40% of the concentration in the formaldehyde test material per square centimetre. Reactions were scored following the ICDRG guidelines. All patients with a +, ++, or +++ reaction to formaldehyde, quaternium-15, or both were included in the study. Statistical analysis was performed by means of the chi-square test with continuity correction, Fisher's exact test (where numbers were small and expected values <5), and Spearman's correlation using SPSS®-16.

Results

In the period 1994–2009, 6503 patients were patch tested with the European baseline series because of suspected contact dermatitis, 3980 women (61%) and 2523 men (39%). There were 86 positive reactions to formaldehyde (1.3%), 70 in women (1.8%) and 16 (0.6%) in men. A total of 107 patients (1.6%) reacted to quaternium-15, 88 in women (2.2%) and 19 (0.8%) in men. Of the 86 formaldehyde-allergic patients, 63 (73%) reacted to quaternium-15; conversely, of the 107 patients allergic to quaternium-15, 63 (59%) co-reacted to formaldehyde. Thus, 130 patients are included in this study, of which 23 reacted to formaldehyde only and 44 to quaternium-15 only; 63 patients reacted to both allergens.

The relationship in these patients between the strength of the reaction to formaldehyde and the number of positive reactions to quaternium-15 is shown in Table 1. Of 65 patients with a + reaction to formaldehyde, 68% co-reacted to quaternium-15. For the group of the stronger ++ formaldehyde reaction, the percentage quaternium-15 co-reactivity was 90 (difference not significant; χ^2, $P = 0.08$). In women co-reactivity of quaternium-15 was 78% in the + formaldehyde group versus 99% in the ++/+++ group (difference not significant; χ^2, $P = 0.2$). In the group of men, there were also no statistical differences between the two groups (+, ++) (Fisher's exact test, $P = 0.5$), but all percentages were substantially lower than in the group of women.

We also investigated the possible inverse relationship between the strength of the reaction to quaternium-15 and the number of formaldehyde co-reactions (Table 2). In the group of 74 patients with a + reaction to quaternium-15, 50% co-reacted to formaldehyde. In the combined ++ and +++ groups, this percentage was 79; the difference is significant (χ^2, $P = 0.01$). In the group of women, co-reactivity was 55% in the + group, and 89% in the stronger (++/+++) reactors. The difference is significant (χ^2, $P = 0.004$). In men, co-reactivity was lower (26%) with no differences between the + and ++ groups.

Finally, we examined the relationship between the strength of the patch test reactions between formaldehyde and quaternium-15 and *vice versa* in the patients reacting to both allergens (Table 3). The majority (82%) of 44 patients with a + reaction to formaldehyde also had a + reaction to

Table 1. Relationship between the strength of patch test reactions to formaldehyde and the number of reactions to quaternium-15

Strength of formaldehyde patch test	Number of patients	Number of patients co-reacting to quaternium-15(%)	
Women and Men			
+	65	44	(68)
++	21	19	(90)
+++	–		–
All Women and Men	86	63	(73)
Women			
+	51	40	(78)
++	19	18	(99)
+++	–		–
All Women	70	58	(83)
Men			
+	14	4	(29)
++	2	1	(50)
+++	–	–	
All Men	16	5	(31)

Table 2. Relationship between the strength of patch test reactions to quaternium-15 and the number of reactions to formaldehyde

Strength of quaternium-15 patch test	Number of patients	Number of patients co-reacting to formaldehyde (%)	
Women and Men			
+	74	37	(50)
++	32	25	(78)
+++	1	1	(100)
All Women and Men	107	63	(59)
Women			
+	60	33	(55)
++	27	24	(89)
+++	1	1	(100)
All Women	88	58	(66)
Men			
+	14	4	(29)
++	5	1	(20)
+++	–	–	
All Men	19	5	(26)

Table 3. Relationship between strengths of reactions to formaldehyde and quaternium-15 in 63 patients reacting to both allergens

Strength of formaldehyde reaction and number of patients		Reactions to quaternium-15		
		+ Number (%)	++ Number (%)	+++ Number (%)
+	44	36 (82)	7 (16)	1 (2)
++	19	1 (5)	18 (95)	–
+++	–	–	–	–
Strength of quaternium-15 reaction and number of patients		**Reactions to formaldehyde**		
		+ Number (%)	++ Number (%)	+++ Number (%)
+	37	36 (97)	1 (3)	–
++	25	7 (28)	18 (72)	–
+++	1	1 (100)		

quaternium-15, and only 18% had a stronger + + or +++ reaction. Of the 19 patients with a + + formaldehyde reaction, however, as much as 95% also had a ++ reaction to quaternium-15. The same pattern was observed in patients allergic to quaternium-15: all but one patient with a + reaction to quaternium-15 had the same strength score to formaldehyde, whereas 72% of the patients with a ++ reaction to quaternium-15 also had a ++ reaction to formaldehyde. The correlation between the + reactions and the ++ reactions from and to both chemicals were statistically significant (Spearman's rho = 0.7).

Discussion

The relationship between positive patch tests to quaternium-15 and other formaldehyde-releasers such as 2-bromo-2-nitropropane-1,3-diol, imidazolidinyl urea, DMDM hydantoin, and diazolidinyl urea and contact allergy to formaldehyde is well known: 15–60% of patients with a reaction to the releasers co-react to formaldehyde. These reactions in formaldehyde-sensitive individuals may well be caused by formaldehyde that is either present in the patch test materials (if at all in a petrolatum vehicle) or released from it by hydrolysis in the water-containing skin (1). So whether a patient allergic to formaldehyde will also react to a formaldehyde-releaser, i.e. reaches the threshold for elicitation of allergic contact dermatitis (the positive patch test), may be largely dependent on the amount of free and releasable formaldehyde in the patch test material and the degree of formaldehyde sensitivity of the patient. Indeed, formaldehyde-releasers used as cosmetic preservatives that contain or release little formaldehyde, such as 2-bromo-2-nitropropane-1,3-diol, show far less co-reactivity to formaldehyde (15%) than donors with higher release such as quaternium-15 (for which the theoretically releasable concentration of formaldehyde in the TRUE test material is approximately 40% of that in the formaldehyde patch) and diazolidinyl urea (>50%) (1). The same applies to formaldehyde-releasers used as durable press chemical finishes, where most reactions in formaldehyde-allergic individuals are observed to the older finishes, which are known to release large amounts of formaldehyde (3, 4). Regarding the strength of the sensitivity, although it is to be expected that the strength of the formaldehyde contact allergy (as expressed by the patch test reaction score, +, ++ or +++) will influence whether formaldehyde-sensitive patients will also react to one or more releasers, there are few data to corroborate this hypothesis. In fact, in only one study have the relationship between the strength of positive patch tests to formaldehyde and patch test reactions to a formaldehyde-releaser been investigated in detail (5). De Groot et al. patch tested 35 patients allergic to formaldehyde with formaldehyde and DMDM hydantoin (two molecules formaldehyde) or MDM hydantoin (one molecule formaldehyde). Test concentrations were 0.1–0.3–1% for formaldehyde and 0.3–1–3% for DMDM hydantoin and MDM hydantoin, respectively. Eight of 14 (57%) formaldehyde-sensitive patients reacted to DMDM hydantoin, whereas only 7 of 21 patients (33%) reacted to MDM hydantoin, which contains less formaldehyde. Most *negative* reactions to DMDM and MDM hydantoin were observed in patients reacting only to the 1% solution of formaldehyde. Patients with 'stronger' allergies to formaldehyde (reacting not only to 1% but also to 0.1% and/or 0.3% formaldehyde) showed more positive reactions, even to the lower concentrations of (D)MDM hydantoin (5).

Aalto-Korte et al. (6) tested a large number of formaldehyde-releasers used in cosmetics and metalworking fluids in patients allergic to formaldehyde and noted that the patients reacting to lower concentrations of formaldehyde in a dilution series tended to have allergic reactions to a larger number of releasers. Twenty-nine patients positive to 1% but negative to 0.1% formaldehyde had a median of one positive reaction to a releaser, whereas in the group of patients reacting to 0.1% with a ++ reaction, the median of positive releasers was four (6).

Some of the data in our study seem to confirm our hypothesis that patients with stronger reactions to formaldehyde (++ or +++) co-react more often to quaternium-15 than in the case of weaker reactions (+), attesting to the causative role of formaldehyde in the positive quaternium-15 patch test. In women,

more positive patch test reactions to quaternium-15 were observed in the subgroup with a stronger ++ reaction to formaldehyde (99%) than in the group with a weaker (+ reaction) sensitivity (78%). The reverse situation in this group shows the same pattern: stronger (++) reactions to quaternium-15 are more often associated with formaldehyde contact allergy (89%) than in the weaker reactor group (55%). In addition, there is even a clear-cut relationship between the strength of the reactions to both allergens: in groups with a + reaction to either chemical, 82–97% has an equally weak + reaction to the other and in the ++ groups, the other allergen also has a ++ reaction in approximately 72–95% of the cases. This also argues in favour of a role for formaldehyde sensitivity.

It is often stated that contact allergy to quaternium-15 can result from sensitivity to formaldehyde, to the entire molecule or to the combination of both (7–11). In our quaternium-15 allergic population, 44 of 107 (41%) had no reaction to formaldehyde, which would indeed suggest an allergic reaction to the entire molecule. However, this concept of quaternium-15 allergy has actually never been proven (only concluded from negative reactions to formaldehyde), nor that a reaction to quaternium-15 can be the result of formaldehyde sensitivity *combined with* contact allergy to quaternium-15 *per se*. The kinetics of the passage of quaternium-15 from the patch test material into and through the skin is unknown. A maximum of six formaldehyde molecules/mole quaternium-15 can be split off, and we know that it releases formaldehyde readily, depending on the pH (1). This means that it is likely that most 'entire' quaternium-15 molecules will lose one or more methylol groups from hydrolysis in the skin. Also, quaternium-15 sensitivity probably results from the use of cosmetic products in the majority of cases. The cosmetics and personal care products that need preservation all contain water and in such products, formaldehyde-release by hydrolysis is highly likely and indeed – for reasons of antimicrobial activity – desirable. One might well argue that these two facts would make the concept of allergy to the *entire* quaternium-15 molecule (with its six methylol groups intact) rather unlikely.

A novel and unexpected finding in this study is a sex-related difference in the relationship between formaldehyde and quaternium-15 contact allergy. Of the women with formaldehyde allergy, 83% also reacted to quaternium-15, but this percentage in men was only 31. This does not appear to be related to differences in strengths of reactions to formaldehyde: the relative sizes of the groups with + and ++ reactions in men and women are largely comparable and the percentage is less in men in each group. In other words, men with formaldehyde allergy are far less likely to have a positive patch test to quaternium-15 than women, even with the same strength formaldehyde reaction. The reason for this is unknown, but when this finding is confirmed by others (many centres should have necessary data), it would contradict our earlier conclusion that (together with the strength of formaldehyde sensitivity) it is mainly the amount of free or releasable formaldehyde in the patch test material that determines whether a positive patch test reaction to a releaser will emerge, as this amount should be the same for both men and women. Conversely, 66% of women allergic to quaternium-15 co-react to formaldehyde versus 26% in men, i.e. in men a smaller part reacting to quaternium-15 is also allergic to formaldehyde. Different exposures might lead to different patterns of sensitization (e.g. sensitization to quaternium-15 in cosmetics might often be accompanied by formaldehyde reactivity), but with our data we were unable to substantiate this, for which further investigations are needed. Simultaneous dose–response testing with formaldehyde and quaternium-15 may provide valuable insight into the relationship between allergy to formaldehyde and patch test co-reactivity to quaternium-15.

Conclusions

Over 80% of women with contact allergy to formaldehyde (TRUE test) also react to the formaldehyde-releaser quaternium-15, and stronger patch test reactivity to formaldehyde increases the likelihood of positive quaternium-15 co-reactions. The strength of the reaction to formaldehyde closely correlates with the strength of the quaternium-15 patch tests. These data are in favour of a very important causative role for formaldehyde in quaternium-15 patch test reactions. For unknown reasons, the correlation between formaldehyde and quaternium-15 in men is substantially less.

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